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FILE 'MEDLINE' ENTERED AT 13:41:01 ON 07 MAY 2008

=> s VNP40110M  
L1 0 VNP40110M

=> s methylaminocarbonyl(a)hydrazine  
L2 17 METHYLAMINOCARBONYL(A) HYDRAZINE

=> s 12 and VNP40101M  
L3 17 L2 AND VNP40101M

=> s 13 and (tumor or antitumor)  
L4 17 L3 AND (TUMOR OR ANTITUMOR)

=> s 14 and nucleoside  
L5 2 L4 AND NUCLEOSIDE

=> dis 14 1-17 bib abs

L4 ANSWER 1 OF 17 CAPLUS COPYRIGHT 2008 ACS on STN

AN 2005:1354137 CAPLUS

DN 144:381446

TI The antineoplastic efficacy of the prodrug Cloretazine is produced by the synergistic interaction of carbamoylating and alkylating products of its activation

AU Baumann, Raymond P.; Seow, Helen A.; Shyam, Krishnamurthy; Penketh, Philip G.; Sartorelli, Alan C.

CS Department of Pharmacology and Developmental Therapeutics Program, Cancer Center, Yale University of Medicine, New Haven, CT, 06520, USA

SO Oncology Research (2005), 15(6), 313-325

CODEN: ONREE8; ISSN: 0965-0407

PB Cognizant Communication Corp.

DT Journal

LA English

AB Cloretazine {1,2-bis(methylsulfonyl)-1-[(2-chloroethyl)-2-(methylamino)carbonyl]hydrazine; VNP40101M; 101M} is a sulfonylhydrazine prodrug that possesses broad spectrum antitumor efficacy against transplanted murine and human tumor models and has shown activity in clin. trials against relapsed or refractory acute myeloid leukemia. Base catalyzed activation of this prodrug generates two different reactive intermediates: chloroethylating species that covalently interact with DNA at the O6-position of guanine residues that progress to a G-C interstrand cross-link, and a carbamoylating agent, Me isocyanate. Previous findings from this laboratory have provided initial evidence that Me isocyanate can contribute to the efficacy of Cloretazine by enhancing the cytotoxicity of the generated chloroethylating species. This action may be due in part to inhibition of the DNA repair protein O6-alkylguanine-DNA alkyltransferase (AGT); however, activity in cells devoid of AGT indicates that other actions are involved in the synergistic cytotoxicity. Herein we demonstrate that O6-benzylguanine can also produce synergistic cell kill with the alkylating component of Cloretazine but differs from Me isocyanate in that the enhancement occurs in AGT-containing cells, but not in cells devoid of AGT. Me isocyanate generated by the decomposition of 1,2-bis(methylsulfonyl)-1-[methylaminocarbonyl]hydrazine also acts to enhance the activity of a variety of DNA crosslinking agents, while only producing additive cytotoxicity with methylating agents. How cytometric studies using annexin as a marker for apoptosis indicate that in Chinese hamster ovary cells and in human leukemia cells Cloretazine-induced apoptosis is primarily caused by the generated Me isocyanate. Comet assays designed to detect DNA cross-links in intact cells indicate that the chloroethylating species generated by the activation of Cloretazine produce DNA cross-links, with the co-generated Me isocyanate increasing the degree of crosslinking produced by the reactive chloroethylating species. These findings provide further evidence that the Me isocyanate produced by the activation of Cloretazine can be a major contributor to the cytotoxicity produced by this antineoplastic agent.

RE.CNT 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 2 OF 17 CAPLUS COPYRIGHT 2008 ACS ON STN

AN 2002:304344 CAPLUS

DN 137:288588

TI Toxicological evaluation of 1,2-bis(methylsulfonyl)-1-(2-chloroethyl)-2-(methylaminocarbonyl)hydrazine (VNP40101M), a novel alkylating agent with potential antitumor activity, with intravenous administration in rats and dogs

AU Lee, King C.; Almassian, Bijan; Noveroske, James

CS Vion Pharmaceuticals, Inc., New Haven, CT, USA

SO International Journal of Toxicology (2002), 21(1), 23-38

CODEN: IJTOFN; ISSN: 1091-5818

PB Taylor & Francis Ltd.

DT Journal

LA English

AB These studies investigated the toxicol. effects of 1,2-bis(methylsulfonyl)-1-(2-chloroethyl)-2-(methylaminocarbonyl) hydrazine, VNP40101M, a novel alkylating antitumor agent, in animals. Sprague-Dawley rats (2-10/sex/time point at each dose) and Beagle dogs (1-3/sex/time point at each dose) were treated with VNP40101M (0 [vehicle], 1, 3, 10, and 20 mg/kg in rats and 0, 0.3, 1, and 3 mg/kg in dogs), given i.v. (IV, bolus via the tail or slow push via the cephalic or saphenous vein, resp.) once daily for 5 consecutive days. Clin. signs, mortality, body weight, clin. pathol., gross necropsy, organ wts., and histopathol. were evaluated for as long as 43 days in rats and 50 days in dogs. In rats, the toxic doses were found to be at 10 and 20 mg/kg, which induced mainly pulmonary toxicity and mortality. The pulmonary toxicity was reflected by an increase in lung weight; clear, pink or red fluid within the thoracic cavity observed at necropsy; and histopathol. evidence of alveolar edema, vascular congestion, alveolar histiocytosis, and vascular thrombi. Although some of these effects were observed in rats treated with 3 mg/kg, the incidence was low (.apprx.7%-30%) and may be reversible (based on the time-dependent reduction in the magnitude of lung weight increases). Therefore, the maximum tolerated dose (MTD, or the maximum dose that did not induce significant toxicity or induced reversible toxicity) was  $\geq 3$  mg/kg. VNP40101M at 1 mg/kg did not induce any toxicity, other than low incidence of alveolar edema (2/30 rats), and increased incidences of capillary ectasis/congestion and alveolar histiocytosis (2-6/30 rats vs. 1/30-36 in control rats). Therefore, the low effect level (LOEL) is considered to be 1 mg/kg in rats when given IV for 5 days. In dogs, LOEL, MTD, and toxic dose levels were comparable (based on a body weight/surface area conversion) to those in rats, except for some gastrointestinal (GI) effects (i.e., red lesion in the ileum) observed at 0.3 mg/kg (equivalent to 1 mg/kg, or similar to the LOEL in rats) and the associated effects (slight body weight loss and inappetence).

For dogs treated with 1 mg/kg (equivalent to .apprx.3 mg/kg, or MTD, in rats), VNP40101M induced the same GI effects seen in dogs treated with 0.3 mg/kg of VNP40101M. Addnl., a transient reduction in white blood cell counts was also observed. Three mg/kg (equivalent to .apprx.10 mg/kg,

or toxic dose level, in rats) was toxic to dogs, as reflected by the poor clin. condition of these dogs, which subsequently required euthanasia. In conclusion, VNP40101M, when given IV once daily for 5 consecutive days, has a LOEL of 1 mg/kg, a MTD of 3 mg/kg, and toxic doses at  $\geq 10$  mg/kg in rats. The primary toxicity of VNP40101M was pulmonary toxicity and mortality. Based on an interspecies body weight/surface area conversion, VNP40101M had comparable LOEL (0.3 mg/kg), MTD (1 mg/kg), and toxic doses ( $\geq 3$  mg/kg) in dogs, except that dogs appeared to be more sensitive to the GI effects of VNP40101M.

RE.CNT 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD  
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on STN

AN 2006-0030302 PASCAL

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TIEN The antineoplastic efficacy of the prodrug Cloretazine is produced by the synergistic interaction of carbamoylating and alkylating products of its activation

AU BAUMANN Raymond P.; SEOW Helen A.; SHYAM Krishnamurthy; PENKETH Philip G.; SARTORELLI Alan C.

CS Department of Pharmacology and Developmental Therapeutics Program, Cancer Center, Yale University School of Medicine, New Haven, CT 06520, United States

SO Oncology research, (2005), 15(6), 313-325, 25 refs.  
ISSN: 0965-0407

DT Journal

BL Analytic

CY United States

LA English

AV INIST-21955, 354000135061190040

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AB Cloretazine 1,2-bis(methylsulfonyl)-1-[(2-chloroethyl)-2-(methylamino)carbonyl]hydrazine; VNP40101M; 101M is a sulfonylhydrazine prodrug that possesses broad spectrum antitumor efficacy against transplanted murine and human tumor models and has shown activity in clinical trials against relapsed or refractory acute myeloid leukemia. Base catalyzed activation of this prodrug generates two different reactive intermediates: chloroethylating species that covalently interact with DNA at the O.sup.6-position of guanine residues that progress to a G-C interstrand cross-link, and a carbamoylating agent, methyl isocyanate. Previous findings from this laboratory have provided initial evidence that methyl isocyanate can contribute to the efficacy of Clore-tazine by enhancing the cytotoxicity of the generated chloroethylating species. This action may be due in part to inhibition of the DNA repair protein O.sup.6-alkylguanine-DNA alkyltransferase (AGT); however, activity in cells devoid of AGT indicates that other actions are involved in the synergistic cytotoxicity. Herein we demonstrate that O.sup.6-benzylguanine can also produce synergistic cell kill with the alkylating component of Cloretazine but differs from methyl isocyanate in that the enhancement occurs in AGT-containing cells, but not in cells devoid of AGT. Methyl isocyanate generated by the decomposition of 1,2-bis(methylsulfonyl)-1-[methylaminocarbonyl]hydrazine also acts to enhance the activity of a variety of DNA cross-linking agents, while only producing additive cytotoxicity with methylating agents. Flow cytometric studies using annexin as a marker for apoptosis indicate that in Chinese hamster ovary cells and in human leukemia cells Cloretazine-induced apoptosis is primarily caused by the generated methyl isocyanate. Comet assays designed to detect DNA cross-links in intact cells indicate that the chloroethylating species generated by the activation of Cloretazine produce DNA cross-links, with the co-generated methyl isocyanate increasing the degree of cross-linking produced by the reactive chloroethylating species. These findings provide further evidence that the methyl isocyanate produced by the activation of Cloretazine can be a major contributor to the cytotoxicity produced by this antineoplastic agent.

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AN 2002-0285439 PASCAL

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TIEN Toxicological evaluation of 1,2-bis(methylsulfonyl)-1-(2-chloroethyl)-2-(methylaminocarbonyl)hydrazine (VNP40101M), a novel alkylating agent with potential antitumor activity, with intravenous administration in rats and dogs

AU LEE King C.; ALMASSIAN Bijan; NOVEROSKE James

CS Vion Pharmaceuticals, Inc., New Haven, Connecticut, United States; Oread Inc., Farmington, Connecticut, United States

SO International journal of toxicology, (2002), 21(1), 23-38, 6 refs.  
ISSN: 1091-5818

DT Journal

BL Analytic  
 CY United Kingdom  
 LA English  
 AV INIST-20351, 354000100837080030  
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 AB These studies investigated the toxicological effects of  
 1,2-bis(methylsulfonyl)-1-(2-chloroethyl)-2-(methylaminocarbonyl  
 ) hydrazine, VNP40101M, a novel alkylating  
 antitumor agent, in animals. Sprague-Dawley rats (2-10/sex/time  
 point at each dose) and Beagle dogs (1-3/sex/time point at each dose)  
 were treated with VNP40101M (0 [vehicle], 1, 3, 10, and 20  
 mg/kg in rats and 0, 0.3, 1, and 3 mg/kg in dogs), given intravenously  
 (IV, bolus via the tail or slow push via the cephalic or saphenous vein,  
 respectively) once daily for 5 consecutive days. Clinical signs,  
 mortality, body weight, clinical pathology, gross necropsy, organ  
 weights, and histopathology were evaluated for as long as 43 days in rats  
 and 50 days in dogs. In rats, the toxic doses were found to be at 10 and  
 20 mg/kg, which induced mainly pulmonary toxicity and mortality. The  
 pulmonary toxicity was reflected by an increase in lung weight; clear,  
 pink or red fluid within the thoracic cavity observed at necropsy; and  
 histopathological evidence of alveolar edema, vascular congestion,  
 alveolar histiocytosis, and vascular thrombi. Although some of these  
 effects were observed in rats treated with 3 mg/kg, the incidence was low  
 (.eqvsim.7%-30%) and may be reversible (based on the time-dependent  
 reduction in the magnitude of lung weight increases). Therefore, the  
 maximum tolerated dose (MTD, or the maximum dose that did not induce  
 significant toxicity or induced reversible toxicity) was  $\geq 3$  mg/kg.  
 VNP40101M at 1 mg/kg did not induce any toxicity, other than low  
 incidence of alveolar edema (2/30 rats), and increased incidences of  
 capillary ectasis/congestion and alveolar histiocytosis (2-6/30 rats vs.  
 1/30-36 in control rats). Therefore, the low effect level (LOEL) is  
 considered to be 1 mg/kg in rats when given IV for 5 days. In dogs, LOEL,  
 MTD, and toxic dose levels were comparable (based on a body  
 weight/surface area conversion) to those in rats, except for some  
 gastrointestinal (GI) effects (i.e., red lesion in the ileum) observed at  
 0.3 mg/kg (equivalent to 1 mg/kg, or similar to the LOEL in rats) and the  
 associated effects (slight body weight loss and inappetence). For dogs  
 treated with 1 mg/kg (equivalent to .eqvsim.3 mg/kg, or MTD, in rats),  
 VNP40101M induced the same GI effects seen in dogs treated with  
 0.3 mg/kg of VNP40101M. Additionally, a transient reduction in  
 white blood cell counts was also observed. Three mg/kg (equivalent to  
 .eqvsim.10 mg/kg, or toxic dose level, in rats) was toxic to dogs, as  
 reflected by the poor clinical condition of these dogs, which  
 subsequently required euthanasia. In conclusion, VNP40101M,  
 when given IV once daily for 5 consecutive days, has a LOEL of 1 mg/kg, a  
 MTD of 3 mg/kg, and toxic doses at  $\geq 10$  mg/kg in rats. The primary  
 toxicity of VNP40101M was pulmonary toxicity and mortality.  
 Based on an interspecies body weight/surface area conversion,  
 VNP40101M had comparable LOEL (0.3 mg/kg), MTD (1 mg/kg), and  
 toxic doses ( $>3$  mg/kg) in dogs, except that dogs appeared to be more  
 sensitive to the GI effects of VNP40101M.

L4 ANSWER 5 OF 17 SCISEARCH COPYRIGHT (c) 2008 The Thomson Corporation on  
 STN  
 AN 2005:1228330 SCISEARCH  
 GA The Genuine Article (R) Number: 989TF  
 TI The antineoplastic efficacy of the prodrug Cloretazine (TM) is produced by  
 the synergistic interaction of carbamoylating and alkylating products of  
 its activation  
 AU Baumann R P; Seow H A; Shyam K; Penketh P G; Sartorelli A C (Reprint)  
 CS Yale Univ, Sch Med, Dept Pharmacol, 333 Cedar St, New Haven, CT 06520 USA

(Reprint); Yale Univ, Sch Med, Dept Pharmacol, New Haven, CT 06520 USA;  
Yale Univ, Sch Med, Dev Therapeut Program, Ctr Canc, New Haven, CT 06520  
USA

alan.sartorelli@yale.edu

CYA USA

SO ONCOLOGY RESEARCH, (2005) Vol. 15, No. 6, pp. 313-325.

ISSN: 0965-0407.

PB COGNIZANT COMMUNICATION CORP, 3 HARTSDALE ROAD, ELMSFORD, NY 10523-3701  
USA.

DT Article; Journal

LA English

REC Reference Count: 25

ED Entered STN: 15 Dec 2005

Last Updated on STN: 15 Dec 2005

\*ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS\*

AB Cloretazine (TM) {1,2-bis(methylsulfonyl)-1-[(2-chloroethyl)-2-(methylamino)carbonyl]hydrazine; VNP40101M; 101M)} is a sulfonylhydrazine prodrug that possesses broad spectrum antitumor efficacy against transplanted murine and human tumor models and has shown activity in clinical trials against relapsed or refractory acute myeloid leukemia. Base catalyzed activation of this prodrug generates two different reactive intermediates: chloroethylating species that covalently interact with DNA at the O-6-position of guanine residues that progress to a G-C interstrand cross-link, and a carbamoylating agent, methyl isocyanate. Previous findings from this laboratory have provided initial evidence that methyl isocyanate can contribute to the efficacy of Cloretazine (TM) by enhancing the cytotoxicity of the generated chloroethylating species. This action may be due in part to inhibition of the DNA repair protein O-6-alkylguanine-DNA alkyltransferase (AGT); however, activity in cells devoid of AGT indicates that other actions are involved in the synergistic cytotoxicity. Herein we demonstrate that O-6-benzylguanine can also produce synergistic cell kill with the alkylating component of Cloretazine (TM) but differs from methyl isocyanate in that the enhancement occurs in AGT-containing cells, but not in cells devoid of AGT. Methyl isocyanate generated by the decomposition of 1,2-bis(methylsulfonyl)-1-[methylaminocarbonyl]hydrazine also acts to enhance the activity of a variety of DNA cross-linking agents, while only producing additive cytotoxicity with methylating agents. How cytometric studies using annexin as a marker for apoptosis indicate that in Chinese hamster ovary cells and in human leukemia cells Cloretazine (TM)-induced apoptosis is primarily caused by the generated methyl isocyanate. Comet assays designed to detect DNA cross-links in intact cells indicate that the chloroethylating species generated by the activation of Cloretazine (TM) produce DNA cross-links, with the co-generated methyl isocyanate increasing the degree of cross-linking produced by the reactive chloroethylating species. These findings provide further evidence that the methyl isocyanate produced by the activation of Cloretazine (TM) can be a major contributor to the cytotoxicity produced by this antineoplastic agent.

L4 ANSWER 6 OF 17 SCISEARCH COPYRIGHT (c) 2008 The Thomson Corporation on  
STN

AN 2002:257851 SCISEARCH

GA The Genuine Article (R) Number: 531HV

TI Toxicological evaluation of 1,2-bis(methylsulfonyl)-1-(2-chloroethyl)-2-(methylaminocarbonyl) hydrazine (VNP40101M), a novel alkylating agent with potential antitumor activity, with intravenous administration in rats and dogs

AU Lee K C (Reprint); Almassian B; Noveroske J

CS Alton Pharma Inc, 777 Old Saw Mill River Rd, Tarrytown, NY 10591 USA  
(Reprint); Vion Pharmaceut Inc, New Haven, CT USA; Oread Inc, Farmington,

CYA CT USA  
 SO USA  
 SO INTERNATIONAL JOURNAL OF TOXICOLOGY, (JAN 2002) Vol. 21, No. 1, pp. 23-38.  
 ISSN: 1091-5818.  
 PB TAYLOR & FRANCIS INC, 325 CHESTNUT ST, SUITE 800, PHILADELPHIA, PA 19106  
 USA.  
 DT Article; Journal  
 LA English  
 REC Reference Count: 6  
 ED Entered STN: 5 Apr 2002  
 Last Updated on STN: 5 Apr 2002  
 \*ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS\*

AB These studies investigated the toxicological effects of 1,2-bis(methylsulfonyl)-1-(2-chloroethyl)-2-(methyaminocarbonyl) hydrazine, VNP40101M, a novel alkylating antitumor agent, in animals. Sprague-Dawley rats (2-10/sex/time point at each dose) and Beagle dogs (1-3/sex/time point at each dose) were treated with VNP40101M (0 [vehicle], 1, 3, 10, and 20 mg/kg in rats and 0, 0.3, 1, and 3 mg/kg in dogs), given intravenously (IV, bolus via the tail or slow push via the cephalic or saphenous vein, respectively) once daily for 5 consecutive days. Clinical signs, mortality, body weight, clinical pathology, gross necropsy, organ weights, and histopathology were evaluated for as long as 43 days in rats and 50 days in dogs. In rats, the toxic doses were found to be at 10 and 20 mg/kg, which induced mainly pulmonary toxicity and mortality. The pulmonary toxicity was reflected by an increase in lung weight; clear, pink or red fluid within the thoracic cavity observed at necropsy; and histopathological evidence of alveolar edema, vascular congestion, alveolar histiocytosis, and vascular thrombi. Although some of these effects were observed in rats treated with 3 mg/kg, the incidence was low (similar to 1-30%) and may be reversible (based on the time-dependent reduction in the magnitude of lung weight increases). Therefore, the maximum tolerated dose (MTD, or the maximum dose that did not induce significant toxicity or induced reversible toxicity) was, 3 mg/kg. VNP40101M at 1 mg/kg did not induce any toxicity, other than low incidence of alveolar edema (2/30 rats), and increased incidences of capillary ectasis/congestion and alveolar histiocytosis (2-6/30 rats vs. 1/30-36 in control rats). Therefore, the low effect level (LOEL) is considered to be 1 mg/kg in rats when given IV for 5 days. In dogs, LOEL, MTD, and toxic dose levels were comparable (based on a body weight/surface area conversion) to those in rats, except for some gastrointestinal (GI) effects (i.e., red lesion in the ileum) observed at 0.3 mg/kg (equivalent to 1 mg/kg, or similar to the LOEL in rats) and the associated effects (slight body weight loss and inappetence). For dogs treated with 1 mg/kg (equivalent to similar to 3 mg/kg, or MTD, in rats), VNP40101M induced the same GI effects seen in dogs treated with 0.3 mg/kg of VNP40101M. Additionally, a transient reduction in white blood cell counts was also observed. Three mg/kg (equivalent to similar to 10 mg/kg, or toxic dose level, in rats) was toxic to dogs, as reflected by the poor clinical condition of these dogs, which subsequently required euthanasia. In conclusion, VNP40101M, when given IV once daily for 5 consecutive days, has a LOEL of 1 mg/kg, a MTD of 3 mg/kg, and toxic doses at, 10 mg/kg in rats. The primary toxicity of VNP40101M was pulmonary toxicity and mortality. Based on an interspecies body weight/surface area conversion, VNP40101M had comparable LOEL (0.3 mg/kg), MTD (1 mg/kg), and toxic doses (greater than or equal to 3 mg/kg) in dogs, except that dogs appeared to be more sensitive to the GI effects of VNP40101M.

L4 ANSWER 7 OF 17 USPATFULL on STN  
 AN 2008:29697 USPATFULL



TI Combination Therapy Comprising Cloretazine  
 IN King, Ivan, North Haven, CT, UNITED STATES  
 Sznol, Mario, Woodbridge, CT, UNITED STATES  
 Belcourt, Michael, Wallingford, CT, UNITED STATES  
 Zheng, Li-Mou, Orange, CT, UNITED STATES  
 PI US 2008025984 A1 20080131  
 AI US 2005-593217 A1 20050325 (10)  
 WO 2005-US10152 20050325  
 20060915 PCT 371 date  
 PRAI US 2004-556565P 20040326 (60)  
 DT Utility  
 FS APPLICATION  
 LREP Law Offices of Albert Wai-Kit Chan, World Plaza, Suite 604, 141-07 20th  
 Avenue, Whitestone, NY, 11357, US  
 CLMN Number of Claims: 22  
 ECL Exemplary Claim: 1  
 DRWN No Drawings  
 LN.CNT 599

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB This invention provides a method for treating tumor in a  
 subject comprising administering to the subject an effective amount of:  
 (1) VNP40101M, or its equivalent; and (2) a nucleoside, or a  
 nucleoside analog. This invention also provides a method for inhibiting  
 tumor cell growth comprising contacting the tumor cell  
 with effective amounts of: (1) VNP40101M, or its equivalent;  
 and (2) a nucleoside, or a nucleoside analog. The present invention  
 relates to the treatment of cancer, comprising administering to a  
 subject in need thereof an effective amount of VNP40101M in  
 combination with a nucleoside.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L4 ANSWER 8 OF 17 USPATFULL on SIN  
 AN 2005:50445 USPATFULL  
 TI Water-soluble SHPs as novel alkylating agents  
 IN Lin, Xu, Branford, CT, UNITED STATES  
 Doyle, Terrence W., Killingworth, CT, UNITED STATES  
 King, Ivan, North Haven, CT, UNITED STATES  
 PA VION PHARMACEUTICALS, INC., New Haven, CT (U.S. corporation)  
 PI US 2005043244 A1 20050224  
 AI US 2004-950890 A1 20040927 (10)  
 RLI Division of Ser. No. US 2003-461282, filed on 13 Jun 2003, PENDING  
 DT Utility  
 FS APPLICATION  
 LREP Henry D. Coleman, 714 Colorado Avenue, Bridgeport, CT, 06605-1601  
 CLMN Number of Claims: 52  
 ECL Exemplary Claim: CLM-01-22  
 DRWN 15 Drawing Page(s)  
 LN.CNT 1684

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention relates to compounds according to the structure  
 (I): ##STR1##

Where R is --CH.sub.3 or --CH.sub.2CH.sub.2Cl; R' is C.sub.1-C.sub.7  
 alkyl or --CH.sub.2CH.sub.2CH.sub.2Cl; R.sub.2 or R.sub.4 is OPO.sub.3H.sub.2,  
 NO.sub.2, OCO(Glu-OH), NHCO(Glu-OH), NHR.sub.7 and unassigned groups of  
 R.sub.2, R.sub.3, R.sub.4, R.sub.5 and R.sub.6 are, independently, H, F,  
 Cl, Br, I, OH, OPO.sub.3H.sub.2, OCH.sub.3, CF.sub.3, OCF.sub.3,  
 NO.sub.2, CN, SO.sub.2CH.sub.3, SO.sub.2CF.sub.3, COCH.sub.3,  
 COOCH.sub.3, SCH.sub.3, SFs, NH.sub.2, NHR.sub.7, N(CH.sub.3).sub.2,  
 OPO.sub.3H.sub.2, or a C1-C7 alkyl group with the proviso that when any

two of unassigned groups of R.sub.2, R.sub.3, R.sub.4, R.sub.5 or R.sub.6 are other than H, the other two of unassigned groups of R.sub.2, R.sub.3, R.sub.4, R.sub.5 or R.sub.6 are H. R.sub.7 is H or polyglutamyl as described. Phosphoric acid and glutamic acid can be a free acid or pharmaceutically acceptable salt thereof.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L4 ANSWER 9 OF 17 USPATFULL on STN  
AN 2004:321449 USPATFULL  
TI WATER-SOLUBLE SHPS AS NOVEL ALKYLATING AGENTS  
IN Lin, Xu, Branford, CT, UNITED STATES  
Doyle, Terrence W., Killingworth, CT, UNITED STATES  
King, Ivan, North Haven, CT, UNITED STATES  
PI US 2004254103 A1 20041216  
US 6855695 B2 20050215  
AI US 2003-461282 A1 20030613 (10)  
DT Utility  
FS APPLICATION  
LREP H.D. Coleman, Coleman Sudol Sapone, P.C., 714 Colorado Avenue,  
Bridgeport, CT, 06605-1601  
CLMN Number of Claims: 73  
ECL Exemplary Claim: 1  
DRWN 15 Drawing Page(s)  
LN.CNT 1745

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention relates to compounds according to the structure  
(I): ##STR1##

Where R is --CH.sub.3 or --CH.sub.2CH.sub.2C1; R' is C.sub.1-C.sub.7 alkyl or --CH.sub.2CH.sub.2C1; R.sub.2 or R.sub.4 is OPO.sub.3H.sub.2, NO.sub.2, OCO(Glu-OH), NHCO(Glu-OH), NHR.sub.7 and unassigned groups of R.sub.2, R.sub.3, R.sub.4, R.sub.5 and R.sub.6 are, independently, H, F, Cl, Br, I, OH, OPO.sub.3H.sub.2, OCH.sub.3, CF.sub.3, OCF.sub.3, NO.sub.2, CN, SO.sub.2CH.sub.3, SO.sub.2CF.sub.3, COCH.sub.3, COOCH.sub.3, SCH.sub.3, SF.sub.5, NH.sub.2, NHR.sub.7, N(CH.sub.3).sub.2, OPO.sub.3H.sub.2, or a C1-C7 alkyl group with the proviso that when any two of unassigned groups of R.sub.2, R.sub.3, R.sub.4, R.sub.5 or R.sub.6 are other than H, the other two of unassigned groups of R.sub.2, R.sub.3, R.sub.4, R.sub.5 or R.sub.6 are H. R.sub.7 is H or polyglutamyl as described. Phosphoric acid and glutamic acid can be a free acid or pharmaceutically acceptable salt thereof.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L4 ANSWER 10 OF 17 USPAT2 on STN  
AN 2004:321449 USPAT2  
TI Water-soluble SHPs as novel alkylating agents  
IN Lin, Xu, Brandford, CT, United States  
Doyle, Terrence W., Killingworth, CT, United States  
King, Ivan, North Haven, CT, United States  
PA Vion Pharmaceuticals, Inc., New Haven, CT, United States (U.S. corporation)  
PI US 6855695 B2 20050215  
AI US 2003-461282 20030613 (10)  
DT Utility  
FS GRANTED  
EXNAM Primary Examiner: Tate, Christopher R.; Assistant Examiner: Ward, Edward  
LREP Coleman, Henry D., Sudol, R. Neil, Sapone, William J.  
CLMN Number of Claims: 73

ECL Exemplary Claim: 1  
DRWN 15 Drawing Figure(s); 15 Drawing Page(s)  
LN.CNT 1735

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention relates to compounds according to the structure  
(I): ##STR1##

Where R is --CH.sub.3 or --CH.sub.2CH.sub.2C1; R' is C.sub.1-C.sub.7  
alkyl or --CH.sub.2CH.sub.2C1; R.sub.2 or R.sub.4 is OPO.sub.3H.sub.2,  
NO.sub.2, OCO(Glu-OH), NHCO(Glu-OH), NHR.sub.7 and unassigned groups of  
R.sub.2, R.sub.3, R.sub.4, R.sub.5 and R.sub.6 are, independently H, F,  
Cl, Br, I, OH, OPO.sub.3H.sub.2, OCH.sub.3, CF.sub.3, OCF.sub.3,  
NO.sub.2, CN, SO.sub.2CH.sub.3, SO.sub.2CF.sub.3, COCH.sub.3,  
COOCH.sub.3, SCH.sub.3, SF.sub.5, NH.sub.2, NHR.sub.7,  
N(CH.sub.3).sub.2, OPO.sub.3H.sub.2, or a C1-C7 alkyl group with the  
proviso that when any two of unassigned groups of R.sub.2, R.sub.3,  
R.sub.4, R.sub.5 or R.sub.6 are other than H, the other two of  
unassigned groups of R.sub.2, R.sub.3, R.sub.4, R.sub.5 or R.sub.6 are  
H. R.sub.7 is H or polyglutamyl as described. Phosphoric acid and  
glutamic acid can be a free acid or pharmaceutically acceptable salt  
thereof.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L4 ANSWER 11 OF 17 WPINDEX COPYRIGHT 2008 THE THOMSON CORP on STN

AN 2005-747008 [76] WPINDEX

DNC C2005-227556 [76]

TI Inhibiting tumor cell growth useful for treating cancer e.g.  
leukemia and lymphoma comprises contacting 1,2-bis(methylsulfonyl)-1-(2-  
chloroethyl)-2-(methylaminocarbonyl) hydrazine (VNP40101M) and nucleoside to the tumor cell

DC B05

IN BELCOURT M; KING I; SZNOL M; ZHENG L; ZHENG L M

PA (VION-N) VION PHARM INC; (BELC-I) BELCOURT M; (KING-I) KING I; (SZNO-I)  
SZNOL M; (ZHEN-I) ZHENG L

CYC 108

PIA WO 2005094282 A2 20051013 (200576)\* EN 19[0]

EP 1804816 A2 20070711 (200746) EN

CN 101014353 A 20070808 (200805) ZH

US 20080025984 A1 20080131 (200810) EN

ADT WO 2005094282 A2 WO 2005-US10152 20050325; CN 101014353 A CN 2005-80009262  
20050325; EP 1804816 A2 EP 2005-745357 20050325; EP 1804816 A2 WO  
2005-US10152 20050325; CN 101014353 A WO 2005-US10152 20050325; US  
20080025984 A1 Provisional US 2004-556565P 20040326; US 20080025984 A1 WO  
2005-US10152 20050325; US 20080025984 A1 US 2006-593217 20060915

FDT EP 1804816 A2 Based on WO 2005094282 A; CN 101014353 A Based on  
WO 2005094282 A

PRAI US 2004-556565P 20040326

US 2006-593217 20060915

AN 2005-747008 [76] WPINDEX

AB WO 2005094282 A2 UPAB: 20060125

NOVELTY - Inhibiting tumor cell growth comprises contacting  
1,2-bis(methylsulfonyl)-1-(2-chloroethyl)-2-(methylaminocarbonyl)  
hydrazine (VNP40101M) or its equivalent and a  
nucleoside or its analog to the tumor cell.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the  
following:

(1) inhibiting tumor cell growth comprising contacting  
VNP40101M or its equivalent; and another anti-tumor  
therapy to the tumor cell; and

(2) a composition comprising VNP40101M in combination

with the nucleoside.

ACTIVITY - Cytostatic.

The cytotoxicity of the combination of VNP40101M (0.75 - 6  $\mu$ M) and AraC (0.75 - 6  $\mu$ M) on L1210 leukemia was examined using a cell viability assay. Cells were exposed to VNP40101M, alone or in combination with various concentrations of AraC. After 72 hours, the remaining viable cells were quantified by measuring mitochondrial oxidoreductase activity. The results showed a combination index of 0.243 after one hour exposure (0.75  $\mu$ M AraC and 6  $\mu$ M VNP40101M used), which indicate strong synergism.

MECHANISM OF ACTION - Tumor cell growth inhibitor.

USE - For treating cancer and tumor (e.g. solid malignant tumor, leukemia (e.g. acute myelogenous leukemia) and lymphoma) (claimed).

ADVANTAGE - The combination of VNP40101M and nucleoside produces synergistic effects in treating tumor.

L4 ANSWER 12 OF 17 BIOSIS COPYRIGHT (c) 2008 The Thomson Corporation on  
STN  
AN 2006:109109 BIOSIS  
DN PREV200600108639  
TI The antineoplastic efficacy of the prodrug Cloretazine (TM) is produced by  
the synergistic interaction of carbamoylating and alkylating products of  
its activation.  
AU Baumann, Raymond P.; Seow, Helen A.; Shyam, Krishnamurthy; Penketh, Philip  
G.; Sartorelli, Alan C. [Reprint Author]  
CS Yale Univ, Sch Med, Dept Pharmacol, 333 Cedar St, New Haven, CT 06520 USA  
alan.sartorelli@yale.edu  
SO Oncology Research, (2005) Vol. 15, No. 6, pp. 313-325.  
CODEN: ONREE8. ISSN: 0965-0407.  
DT Article  
LA English  
ED Entered STN: 8 Feb 2006  
Last Updated on STN: 8 Feb 2006  
AB Cloretazine (TM) {1,2-bis(methylsulfonyl)-1-[(2-chloroethyl)-2-  
(methylamino)carbonyl]hydrazine; VNP40101M; 101M)} is a  
sulfonylhydrazine prodrug that possesses broad spectrum antitumor  
efficacy against transplanted murine and human tumor models and  
has shown activity in clinical trials against relapsed or refractory acute  
myeloid leukemia. Base catalyzed activation of this prodrug generates two  
different reactive intermediates: chloroethylating species that covalently  
interact with DNA at the O-6-position of guanine residues that progress to a  
G-C interstrand cross-link, and a carbamoylating agent, methyl  
isocyanate. Previous findings from this laboratory have provided initial  
evidence that methyl isocyanate can contribute to the efficacy of  
Cloretazine (TM) by enhancing the cytotoxicity of the generated  
chloroethylating species. This action may be due in part to inhibition of  
the DNA repair protein O-6-alkylguanine-DNA alkyltransferase (AGT);  
however, activity in cells devoid of AGT indicates that other actions are  
involved in the synergistic cytotoxicity. Herein we demonstrate that  
O-6-benzylguanine can also produce synergistic cell kill with the  
alkylating component of Cloretazine (TM) but differs from methyl  
isocyanate in that the enhancement occurs in AGT-containing cells, but not  
in cells devoid of AGT. Methyl isocyanate generated by the decomposition  
of 1,2-bis(methylsulfonyl)-1-[(methylaminocarbonyl)  
hydrazine also acts to enhance the activity of a variety of DNA  
cross-linking agents, while only producing additive cytotoxicity with  
methylating agents. How cytometric studies using annexin as a marker for  
apoptosis indicate that in Chinese hamster ovary cells and in human  
leukemia cells Cloretazine (TM)-induced apoptosis is primarily caused by  
the generated methyl isocyanate. Comet assays designed to detect DNA

cross-links in intact cells indicate that the chloroethylating species generated by the activation of Cloretazine (TM) produce DNA cross-links, with the co-generated methyl isocyanate increasing the degree of cross-linking produced by the reactive chloroethylating species. These findings provide further evidence that the methyl isocyanate produced by the activation of Cloretazine (TM) can be a major contributor to the cytotoxicity produced by this antineoplastic agent.

L4 ANSWER 13 OF 17 BIOSIS COPYRIGHT (c) 2008 The Thomson Corporation on  
STN  
AN 2002:291321 BIOSIS  
DN PREV200200291321  
TI Toxicological evaluation of 1,2-bis(methylsulfonyl)-1-(2-chloroethyl)-2-(  
methylaminocarbonyl)hydrazine (VNP40101M), a  
novel alkylating agent with potential antitumor activity, with  
intravenous administration in rats and dogs.  
AU Lee, King C. [Reprint author]; Almassian, Bijan; Noveroske, James  
CS Aton Pharma, Inc., 777 Old Saw Mill River Road, Tarrytown, NY, 10591, USA  
klee@atonpharma.com  
SO International Journal of Toxicology, (January-February, 2002) Vol. 21, No.  
1, pp. 23-38. print.  
ISSN: 1091-5818.  
DT Article  
LA English  
ED Entered STN: 15 May 2002  
Last Updated on STN: 15 May 2002  
AB These studies investigated the toxicological effects of  
1,2-bis(methylsulfonyl)-1-(2-chloroethyl)-2-(methylaminocarbonyl  
) hydrazine, VNP40101M, a novel alkylating  
antitumor agent, in animals. Sprague-Dawley rats (2-10/sex/time  
point at each dose) and Beagle dogs (1-3/sex/time point at each dose) were  
treated with VNP40101M (0 (vehicle), 1, 3, 10, and 20 mg/kg in  
rats and 0, 0.3, 1, and 3 mg/kg in dogs), given intravenously (IV, bolus  
via the tail or slow push via the cephalic or saphenous vein,  
respectively) once daily for 5 consecutive days. Clinical signs,  
mortality, body weight, clinical pathology, gross necropsy, organ weights,  
and histopathology were evaluated for as long as 43 days in rats and 50  
days in dogs. In rats, the toxic doses were found to be at 10 and 20  
mg/kg, which induced mainly pulmonary toxicity and mortality. The  
pulmonary toxicity was reflected by an increase in lung weight; clear,  
pink or red fluid within the thoracic cavity observed at necropsy; and  
histopathological evidence of alveolar edema, vascular congestion,  
alveolar histiocytosis, and vascular thrombi. Although some of these  
effects were observed in rats treated with 3 mg/kg, the incidence was low  
(apprx 7%-30%) and may be reversible (based on the time-dependent reduction  
in the magnitude of lung weight increases). Therefore, the maximum  
tolerated dose (MTD, or the maximum dose that did not induce significant  
toxicity or induced reversible toxicity) was gtoeq3 mg/kg.  
VNP40101M at 1 mg/kg did not induce any toxicity, other than low  
incidence of alveolar edema (2/30 rats), and increased incidences of  
capillary ectasis/congestion and alveolar histiocytosis (2-6/30 rats vs.  
1/30-36 in control rats). Therefore, the low effect level (LOEL) is  
considered to be 1 mg/kg in rats when given IV for 5 days. In dogs, LOEL,  
MTD, and toxic dose levels were comparable (based on a body weight/surface  
area conversion) to those in rats, except for some gastrointestinal (GI)  
effects (i.e., red lesion in the ileum) observed at 0.3 mg/kg (equivalent  
to 1 mg/kg, or similar to the LOEL in rats) and the associated effects  
(slight body weight loss and inappetence). For dogs treated with 1 mg/kg  
(equivalent to apprx 3 mg/kg, or MTD, in rats), VNP40101M induced  
the same GI effects seen in dogs treated with 0.3 mg/kg of  
VNP40101M. Additionally, a transient reduction in white blood

cell counts was also observed. Three mg/kg (equivalent to approx 10 mg/kg, or toxic dose level, in rats) was toxic to dogs, as reflected by the poor clinical condition of these dogs, which subsequently required euthanasia. In conclusion, VNP40101M, when given IV once daily for 5 consecutive days, has a LOEL of 1 mg/kg, a MTD of 3 mg/kg, and toxic doses at 10 mg/kg in rats. The primary toxicity of VNP40101M was pulmonary toxicity and mortality. Based on an interspecies body weight/surface area conversion, VNP40101M had comparable LOEL (0.3 mg/kg), MTD (1 mg/kg), and toxic doses (10 mg/kg) in dogs, except that dogs appeared to be more sensitive to the GI effects of VNP40101M.

L4 ANSWER 14 OF 17 EMBASE COPYRIGHT (c) 2008 Elsevier B.V. All rights reserved on STN  
AN 2006024721 EMBASE  
TI The antineoplastic efficacy of the prodrug cloretazine® is produced by the synergistic interaction of carbamoylating and alkylating products of its activation.  
AU Baumann, Raymond P.; Seow, Helen A.; Shyam, Krishnamurthy; Penketh, Philip G.; Sartorelli, Alan C. (correspondence)  
CS Department of Pharmacology and Developmental Therapeutics Program, Cancer Center, Yale University School of Medicine, New Haven, CT 06520, United States. alan.sartorelli@yale.edu  
AU Sartorelli, Alan C. (correspondence)  
CS Department of Pharmacology, Yale University School of Medicine, 333 Cedar St., New Haven, CT 06520, United States. alan.sartorelli@yale.edu  
SO Oncology Research, (2005) Vol. 15, No. 6, pp. 313-325.  
Refs: 25  
ISSN: 0965-0407 CODEN: ONREE8  
CY United States  
DT Journal; Article  
FS 016 Cancer  
030 Clinical and Experimental Pharmacology  
037 Drug Literature Index  
LA English  
SL English  
ED Entered STN: 26 Jan 2006  
Last Updated on STN: 26 Jan 2006  
AB Cloretazine® {1,2-bis(methylsulfonyl)-1-[(2-chloroethyl)-2-(methylamino)carbonyl]hydrazine; VNP40101M; 101M} is a sulfonylhydrazine prodrug that possesses broad spectrum antitumor efficacy against transplanted murine and human tumor models and has shown activity in clinical trials against relapsed or refractory acute myeloid leukemia. Base catalyzed activation of this prodrug generates two different reactive intermediates: chloroethylating species that covalently interact with DNA at the O(6)-position of guanine residues that progress to a G-C interstrand cross-link, and a carbamoylating agent, methyl isocyanate. Previous findings from this laboratory have provided initial evidence that methyl isocyanate can contribute to the efficacy of Cloretazine® by enhancing the cytotoxicity of the generated chloroethylating species. This action may be due in part to inhibition of the DNA repair protein O(6)-alkylguanine-DNA alkyltransferase (AGT); however, activity in cells devoid of AGT indicates that other actions are involved in the synergistic cytotoxicity. Herein we demonstrate that O(6)-benzylguanine can also produce synergistic cell kill with the alkylating component of Cloretazine® but differs from methyl isocyanate in that the enhancement occurs in AGT-containing cells, but not in cells devoid of AGT. Methyl isocyanate generated by the decomposition of 1,2-bis(methylsulfonyl)-1-[(methylaminocarbonyl]hydrazine also acts to enhance the activity of a variety of DNA cross-linking agents, while only producing additive cytotoxicity with

methyating agents. Flow cytometric studies using annexin as a marker for apoptosis indicate that in Chinese hamster ovary cells and in human leukemia cells Cloretazine®-induced apoptosis is primarily caused by the generated methyl isocyanate. Comet assays designed to detect DNA cross-links in intact cells indicate that the chloroethylating species generated by the activation of Cloretazine® produce DNA cross-links, with the co-generated methyl isocyanate increasing the degree of cross-linking produced by the reactive chloroethylating species. These findings provide further evidence that the methyl isocyanate produced by the activation of Cloretazine® can be a major contributor to the cytotoxicity produced by this antineoplastic agent. Copyright .COPYRGT. 2005 Cognizant Comm. Corp.

L4 ANSWER 15 OF 17 EMBASE COPYRIGHT (c) 2008 Elsevier B.V. All rights reserved on STN  
 AN 2002126943 EMBASE  
 TI Toxicological evaluation of 1,2-Bis(methylsulfonyl)-1-(2-chloroethyl)-2-(methylaminocarbonyl)hydrazine (VNP40101M), a novel alkylating agent with potential antitumor activity, with intravenous administration in rats and dogs.  
 AU Lee, King C., Dr. (correspondence); Almæssian, Bijan; Noveroske, James  
 CS RAC, Aton Pharma, Inc., 777 Old Saw Mill River Road, Tarrytown, NY 10591, United States. klee@atonpharma.com  
 SO International Journal of Toxicology, (2002) Vol. 21, No. 1, pp. 23-38.  
 Refs: 6  
 ISSN: 1091-5818 CODEN: IJTOFN  
 CY United States  
 DT Journal; Article  
 FS 016 Cancer  
 030 Clinical and Experimental Pharmacology  
 037 Drug Literature Index  
 052 Toxicology  
 LA English  
 SL English  
 ED Entered STN: 25 Apr 2002  
 Last Updated on STN: 25 Apr 2002  
 AB These studies investigated the toxicological effects of 1,2-bis(methylsulfonyl)-1-(2-chloroethyl)-2-(methylaminocarbonyl) hydrazine, VNP40101M, a novel alkylating antitumor agent, in animals. Sprague-Dawley rats (2-10/sex/time point at each dose) and Beagle dogs (1-3/sex/time point at each dose) were treated with VNP40101M (0 [vehicle], 1, 3, 10, and 20 mg/kg in rats and 0, 0.3, 1, and 3 mg/kg in dogs), given intravenously (IV, bolus via the tail or slow push via the cephalic or saphenous vein, respectively) once daily for 5 consecutive days. Clinical signs, mortality, body weight, clinical pathology, gross necropsy, organ weights, and histopathology were evaluated for as long as 43 days in rats and 50 days in dogs. In rats, the toxic doses were found to be at 10 and 20 mg/kg, which induced mainly pulmonary toxicity and mortality. The pulmonary toxicity was reflected by an increase in lung weight; clear, pink or red fluid within the thoracic cavity observed at necropsy; and histopathological evidence of alveolar edema, vascular congestion, alveolar histiocytosis, and vascular thrombi. Although some of these effects were observed in rats treated with 3 mg/kg, the incidence was low (.apprx.7%-30%) and may be reversible (based on the time-dependent reduction in the magnitude of lung weight increases). Therefore, the maximum tolerated dose (MTD, or the maximum dose that did not induce significant toxicity or induced reversible toxicity) was ≥3 mg/kg. VNP40101M at 1 mg/kg did not induce any toxicity, other than low incidence of alveolar edema (2/30 rats), and increased incidences of capillary ectasis/congestion and alveolar histocytosis (2-6/30 rats vs.

1/30-36 in control rats). Therefore, the low effect level (LOEL) is considered to be 1 mg/kg in rats when given IV for 5 days. In dogs, LOEL, MTD, and toxic dose levels were comparable (based on a body weight/surface area conversion) to those in rats, except for some gastrointestinal (GI) effects (i.e., red lesion in the ileum) observed at 0.3 mg/kg (equivalent to 1 mg/kg, or similar to the LOEL in rats) and the associated effects (slight body weight loss and inappetence). For dogs treated with 1 mg/kg (equivalent to .apprx.3 mg/kg, or MTD, in rats), VNP40101M induced the same GI effects seen in dogs treated with 0.3 mg/kg of VNP40101M. Additionally, a transient reduction in white blood cell counts was also observed. Three mg/kg (equivalent to .apprx.10 mg/kg, or toxic dose level, in rats) was toxic to dogs, as reflected by the poor clinical condition of these dogs, which subsequently required euthanasia. In conclusion, VNP40101M, when given IV once daily for 5 consecutive days, has a LOEL of 1 mg/kg, a MTD of 3 mg/kg, and toxic doses at  $\geq 10$  mg/kg in rats. The primary toxicity of VNP40101M was pulmonary toxicity and mortality. Based on an interspecies body weight/surface area conversion, VNP40101M had comparable LOEL (0.3 mg/kg), MTD (1 mg/kg), and toxic doses ( $\geq 3$  mg/kg) in dogs, except that dogs appeared to be more sensitive to the GI effects of VNP40101M.

L4 ANSWER 16 OF 17 MEDLINE on STN  
 AN 2006021874 MEDLINE  
 DN PubMed ID: 16408696  
 TI The antineoplastic efficacy of the prodrug Cloretazine is produced by the synergistic interaction of carbamoylating and alkylating products of its activation.  
 AU Baumann Raymond P; Seow Helen A; Shyam Krishnamurthy; Penketh Philip G; Sartorelli Alan C  
 CS Department of Pharmacology and Developmental Therapeutics Program, Cancer Center, Yale University School of Medicine, New Haven, CT 06520, USA.  
 NC CA-90671 (United States NCI)  
 SO Oncology research, (2005) Vol. 15, No. 6, pp. 313-25.  
 Journal code: 9208097. ISSN: 0965-0407.  
 CY United States  
 DT Journal; Article; (JOURNAL ARTICLE)  
 (RESEARCH SUPPORT, N.I.H., EXTRAMURAL)  
 LA English  
 FS Priority Journals  
 EM 200603  
 ED Entered STN: 14 Jan 2006  
 Last Updated on STN: 22 Mar 2006  
 Entered Medline: 21 Mar 2006  
 AB Cloretazine {1,2-bis(methylsulfonyl)-1-[(2-chloroethyl)-2-(methylamino)carbonyl]hydrazine; VNP40101M; 101M} is a sulfonylhydrazine prodrug that possesses broad spectrum antitumor efficacy against transplanted murine and human tumor models and has shown activity in clinical trials against relapsed or refractory acute myeloid leukemia. Base catalyzed activation of this prodrug generates two different reactive intermediates: chloroethylating species that covalently interact with DNA at the O6-position of guanine residues that progress to a G-C interstrand cross-link, and a carbamoylating agent, methyl isocyanate. Previous findings from this laboratory have provided initial evidence that methyl isocyanate can contribute to the efficacy of Cloretazine by enhancing the cytotoxicity of the generated chloroethylating species. This action may be due in part to inhibition of the DNA repair protein O6-alkylguanine-DNA alkyltransferase (AGT); however, activity in cells devoid of AGT indicates that other actions are involved in the synergistic cytotoxicity. Herein we demonstrate that O6-benzylguanine can also produce synergistic cell kill with the



alkylating component of Cloretazine but differs from methyl isocyanate in that the enhancement occurs in AGT-containing cells, but not in cells devoid of AGT. Methyl isocyanate generated by the decomposition of 1,2-bis(methylsulfonyl)-1-[methyaminocarbonyl]hydrazine also acts to enhance the activity of a variety of DNA cross-linking agents, while only producing additive cytotoxicity with methylating agents. Flow cytometric studies using annexin as a marker for apoptosis indicate that in Chinese hamster ovary cells and in human leukemia cells Cloretazine-induced apoptosis is primarily caused by the generated methyl isocyanate. Comet assays designed to detect DNA cross-links in intact cells indicate that the chloroethylating species generated by the activation of Cloretazine produce DNA cross-links, with the co-generated methyl isocyanate increasing the degree of cross-linking produced by the reactive chloroethylating species. These findings provide further evidence that the methyl isocyanate produced by the activation of Cloretazine can be a major contributor to the cytotoxicity produced by this antineoplastic agent.

L4 ANSWER 17 OF 17 MEDLINE on STN  
AN 2002203737 MEDLINE  
DN PubMed ID: 11936896  
TI Toxicological evaluation of 1,2-bis(methylsulfonyl)-1-(2-chloroethyl)-2-(methyaminocarbonyl)hydrazine (VNP40101M), a novel alkylating agent with potential antitumor activity, with intravenous administration in rats and dogs.  
AU Lee King C; Almassian Bijan; Noveroske James  
CS Vion Pharmaceuticals, Inc, New Haven, Connecticut, USA..  
klee@atonpharma.com  
SO International journal of toxicology, (2002 Jan-Feb) Vol. 21, No. 1, pp. 23-38.  
Journal code: 9708436. ISSN: 1091-5818.  
CY United States  
DT (COMPARATIVE STUDY)  
Journal; Article; (JOURNAL ARTICLE)  
LA English  
FS Priority Journals  
EM 200209  
ED Entered STN: 9 Apr 2002  
Last Updated on STN: 6 Sep 2002  
Entered Medline: 5 Sep 2002  
AB These studies investigated the toxicological effects of 1,2-bis(methylsulfonyl)-1-(2-chloroethyl)-2-(methyaminocarbonyl)hydrazine, VNP40101M, a novel alkylating antitumor agent, in animals. Sprague-Dawley rats (2-10/sex/time point at each dose) and Beagle dogs (1-3/sex/time point at each dose) were treated with VNP40101M (0 [vehicle], 1, 3, 10, and 20 mg/kg in rats and 0, 0.3, 1, and 3 mg/kg in dogs), given intravenously (IV, bolus via the tail or slow push via the cephalic or saphenous vein, respectively) once daily for 5 consecutive days. Clinical signs, mortality, body weight, clinical pathology, gross necropsy, organ weights, and histopathology were evaluated for as long as 43 days in rats and 50 days in dogs. In rats, the toxic doses were found to be at 10 and 20 mg/kg, which induced mainly pulmonary toxicity and mortality. The pulmonary toxicity was reflected by an increase in lung weight; clear, pink or red fluid within the thoracic cavity observed at necropsy; and histopathological evidence of alveolar edema, vascular congestion, alveolar histiocytosis, and vascular thrombi. Although some of these effects were observed in rats treated with 3 mg/kg, the incidence was low (approximately 7%-30%) and may be reversible (based on the time-dependent reduction in the magnitude of lung weight increases). Therefore, the maximum tolerated dose (MTD, or the maximum dose that did not induce

significant toxicity or induced reversible toxicity) was  $\geq$  3 mg/kg. VNP40101M at 1 mg/kg did not induce any toxicity, other than low incidence of alveolar edema (2/30 rats), and increased incidences of capillary ectasis/congestion and alveolar histiocytosis (2-6/30 rats vs. 1/30-36 in control rats). Therefore, the low effect level (LOEL) is considered to be 1 mg/kg in rats when given IV for 5 days. In dogs, LOEL, MTD, and toxic dose levels were comparable (based on a body weight/surface area conversion) to those in rats, except for some gastrointestinal (GI) effects (i.e., red lesion in the ileum) observed at 0.3 mg/kg (equivalent to 1 mg/kg, or similar to the LOEL in rats) and the associated effects (slight body weight loss and inappetence). For dogs treated with 1 mg/kg (equivalent to approximately 3 mg/kg, or MTD, in rats), VNP40101M induced the same GI effects seen in dogs treated with 0.3 mg/kg of VNP40101M. Additionally, a transient reduction in white blood cell counts was also observed. Three mg/kg (equivalent to approximately 10 mg/kg, or toxic dose level, in rats) was toxic to dogs, as reflected by the poor clinical condition of these dogs, which subsequently required euthanasia. In conclusion, VNP40101M, when given IV once daily for 5 consecutive days, has a LOEL of 1 mg/kg, a MTD of 3 mg/kg, and toxic doses at  $\geq$  10 mg/kg in rats. The primary toxicity of VNP40101M was pulmonary toxicity and mortality. Based on an interspecies body weight/surface area conversion, VNP40101M had comparable LOEL (0.3 mg/kg), MTD (1 mg/kg), and toxic doses ( $\geq$  3 mg/kg) in dogs, except that dogs appeared to be more sensitive to the GI effects of VNP40101M.

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FULL ESTIMATED COST	115.82	116.24
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	ENTRY	SESSION
CA SUBSCRIBER PRICE	-1.60	-1.60

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 FILE LAST UPDATED: 6 May 2008 (20080506/ED)

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=> s King Ivan/AU

L6 42 KING IVAN/AU

=> s 16 and chloretazine  
0 CHLORETAZINE  
L7 0 L6 AND CHLORETAZINE

=> s 17 and cloretazine  
21 CLORETAZINE  
L8 0 L7 AND CLORETAZINE

=> s 16 and cloretazine  
21 CLORETAZINE  
L9 3 L6 AND CLORETAZINE

=> dis 19 1-3 bib abs

L9 ANSWER 1 OF 3 CAPLUS COPYRIGHT 2008 ACS on STN

AN 2007:922296 CAPLUS

DN 147:356518

TI Activity of VNP40101M (Cloretazine) in the treatment of CNS  
tumor xenografts in athymic mice

AU Badruddoja, Michael A.; Keir, Stephen T.; King, Ivan; Zeidner,  
Joseph; Vredenburgh, James J.; Muhlbaier, Lawrence H.; Bigner, Darell D.;  
Friedman, Henry S.

CS Center for Neurosciences, University of Arizona, Tucson, AZ, 85721, USA

SO Neuro-Oncology (Durham, NC, United States) (2007), 9(3), 240-244

CODEN: NEURJR; ISSN: 1522-8517

PB Duke University Press

DT Journal

LA English

AB VNP40101M, or 1,2-bis(methylsulfonyl)-1-(2-chloro-ethyl)-2-  
(methylamino)carbonylhydrazine (Cloretazine), is a bifunctional  
prodrug that belongs to a class of DNA-modifying agents-the  
sulfonylhydrazines-that has been synthesized and been shown to have  
activity against a wide spectrum of xenografts. The current study was  
designed to assess the activity of VNP40101M administered at a dose of 18  
mg/kg daily for five days against a panel of human adult and pediatric CNS  
tumors growing s.c. or intracranially in athymic nude mice. The results  
demonstrated statistically significant ( $p < 0.05$ ) growth delays of 15.0,  
8.3, 51.0, 60+, 60+, and 60+ days in s.c. xenografts derived from  
childhood glioblastoma multiforme (D-456 MG), childhood ependymoma (D-528  
EP and D-612 EP), childhood medulloblastoma (D-425 MED), and adult  
malignant glioma (D-245 MG and D-54 MG), resp., with corresponding tumor  
regressions in 10 of 10, 4 of 10, 8 of 10, 9 of 10, 9 of 10, and 10 of 10  
treated mice, resp. Delayed toxicity was seen more than 60 days after  
treatment, with 23 deaths in 100 treated animals, despite a median weight  
loss of only 0.06%. In mice bearing intracranial D-245 MG xenografts,  
treatment with VNP40101M at a dose of 18 mg/kg daily for five days  
produced a 50% increase in median survival compared with controls. Addnl.  
expts. conducted against s.c. D-245 MG xenografts by using reduced doses  
of 13.5 or 9.0 mg/kg daily for five days demonstrated tumor growth delays  
of 82.2 and 53.5 days, with corresponding tumor regressions in 8 of 9 and  
9 of 10 treated mice, resp. (all values,  $p < 0.001$ ), with one toxic death.  
These findings suggest that VNP40101M is active in the treatment of a wide  
range of human central nervous system tumors and warrants translation to  
the clinic.

RE.CNT 15 THERE ARE 15 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 2 OF 3 CAPLUS COPYRIGHT 2008 ACS on STN

AN 2007:447320 CAPLUS

DN 147:180783  
 TI Anti-tumor efficacy of Cloretazine (VNP40101M) alone and in combination with fludarabine in murine tumor and human xenograft tumor models  
 AU Zheng, Li-mou; Li, Zujin; Liu, Lanzhen; Song, Bai Louis; King, Ivan  
 CS Vion Pharmaceutical, Inc., New Haven, CT, 06511, USA  
 SO Cancer Chemotherapy and Pharmacology (2007), 60(1), 45-51  
 CODEN: CCPHDZ; ISSN: 0344-5704  
 PB Springer  
 DT Journal  
 LA English  
 AB Cloretazine (VNP40101M), a new sulfonylhydrazine alkylating agent, has demonstrated broad-spectrum anti-tumor activity in preclin. studies. In this study, Cloretazine was evaluated both as a monotherapy and in combination with fludarabine in murine tumor and human tumor xenograft models. Cloretazine significantly inhibited the growth of s.c. implanted tumors, including B16F10 murine melanoma in C57BL/6 mice, and H460 human lung carcinoma and WiDr human colon carcinoma in athymic nude CD1 mice. The inhibition of tumor growth by Cloretazine was dose dependent, increasing from 42.2 to 87% as the dose escalated from 100 to 150 mg/kg. Cloretazine showed equivalent efficacy but lower toxicity compared to cyclophosphamide in these models. The combination therapy, consisting of a single dose of 10 mg/kg Cloretazine plus five doses of 70 mg/kg fludarabine, given every other day i.p., significantly increased the long-term survival of BDF1 mice bearing the L1210 murine leukemia. On Day 65 post-tumor implantation, the combination therapy yielded a 90% survival rate compared to 40% for Cloretazine alone and 0% for fludarabine alone.

RE.CNT 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS RECORD  
 ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 3 OF 3 CAPLUS COPYRIGHT 2008 ACS on SIN  
 AN 2005:1103438 CAPLUS  
 DN 143:360090  
 TI Cloretazinnetm (VNP40101M) combination with a nucleoside/nucleoside analog for cancer treatment  
 IN King, Ivan; Sznol, Mario; Belcourt, Michael; Zheng, Li-Mou  
 PA Vion Pharmaceuticals, Inc., USA  
 SO PCT Int. Appl., 19 pp.  
 CODEN: PIXXD2  
 DT Patent  
 LA English  
 FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2005094282	A2	20051013	WO 2005-US10152	20050325
	WO 2005094282	A3	20060511		
W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW:	BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
EP	1804816	A2	20070711	EP 2005-745357	20050325
	R:	AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE,			

IS, IT, LI, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR  
 CN 101014353 A 20070808 CN 2005-80009262 20050325  
 US 20080025984 A1 20080131 US 2006-593217 20060915  
 PRAI US 2004-556565P P 20040326  
 WO 2005-US10152 W 20050325  
 AB The invention provides a method for treating tumor in a subject comprising administering to the subject an effective amount of (1) VNP40101M, or its equivalent; and (2) a nucleoside, or a nucleoside analog. The invention also provides a method for inhibiting tumor cell growth comprising contacting the tumor cell with effective amts. of: (1) VNP40101M, or its equivalent; and (2) a nucleoside, or a nucleoside analog. The invention relates to the treatment of cancer, comprising administering to a subject in need thereof an effective amount of VNP40101M in combination with a nucleoside.

=> s Sznol Mario/AU  
 L10 30 SZNOL MARIO/AU

=> s l10 and cloretazine  
 21 CLORETAZINE  
 L11 2 L10 AND CLORETAZINE

=> dis l11 1-2 bib abs

L11 ANSWER 1 OF 2 CAPLUS COPYRIGHT 2008 ACS on STN  
 AN 2005:1191211 CAPLUS  
 DN 144:285703  
 TI Phase I Study of Cloretazine (VNP40101M), a Novel  
 Sulfonylhydrazine Alkylating Agent, Combined with Cytarabine in Patients  
 with Refractory Leukemia  
 AU Giles, Francis; Verstovsek, Srdan; Thomas, Deborah; Gerson, Stanton;  
 Cortes, Jorge; Faderl, Stefan; Ferrajoli, Alessandra; Ravandi, Farhad;  
 Kornblau, Steven; Garcia-Manero, Guillermo; Jabbour, Elias; O'Brien,  
 Susan; Karsten, Verena; Cahill, Ann; Yee, Karen; Albitar, Maher;  
 Sznol, Mario; Kantarjian, Hagop  
 CS Department of Leukemia, The University of Texas M.D. Anderson Cancer  
 Center, Houston, TX, USA  
 SO Clinical Cancer Research (2005), 11(21), 7817-7824  
 CODEN: CCRF4; ISSN: 1078-0432  
 PB American Association for Cancer Research  
 DT Journal  
 LA English  
 AB Purpose: Cloretazine (VNP40101M) is a novel sulfonylhydrazine  
 alkylating agent with significant antileukemia activity. A phase I study  
 of cloretazine combined with cytarabine (1-β-D-  
 arabinofuranosylcytosine, ara-C) was conducted in patients with refractory  
 disease. Design: Ara-C was given i.v. at a fixed dose of 1.5 gm/m<sup>2</sup>d by  
 continuous infusion for 4 days (patients ages <65 years at time of  
 diagnosis) or 3 days (patients ages ≥65 years).  
 Cloretazine was given i.v. over 15 to 60 min on day 2 at a  
 starting dose of 200 mg/m<sup>2</sup>, with escalation in 100 mg/m<sup>2</sup> increments in  
 cohorts of three to six patients until a maximum tolerated dose was  
 established. The DNA repair enzyme O6-alkylguanine DNA alkyltransferase  
 (AGT) was measured at baseline. Results: Forty patients, including 32  
 with acute myeloid leukemia, received 47 courses of treatment. Complete  
 responses were seen at cloretazine dose levels of ≥400  
 mg/m<sup>2</sup> in 10 of 37 (27%) evaluable patients, and in this patient subset,  
 AGT activity was significantly lower in patients that responded to  
 treatment than in patients who did not (P ≤ 0.027). Dose-limiting  
 toxicities (gastrointestinal and myelosuppression) were seen with 500 and  
 600 mg/m<sup>2</sup> of cloretazine combined with the 4-day ara-C schedule

but not seen with the 3-day schedule. Conclusion: The recommended cloretazine dose schedule for future studies is 600 mg/m2 combined with 1.5 gm/m2/d continuous infusion of ara-C for 3 days. The cloretazine and ara-C regimen has significant antileukemic activity. AGT activity may be a predictor of response to cloretazine.

RE.CNT 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 2 OF 2 CAPLUS COPYRIGHT 2008 ACS on STN  
AN 2005:1103438 CAPLUS  
DN 143:360090  
TI Cloretazinetm (VNP40101M) combination with a nucleoside/nucleoside analog  
for cancer treatment  
IN King, Ivan; Sznol, Mario; Belcourt, Michael; Zheng, Li-Mou  
PA Vion Pharmaceuticals, Inc., USA  
SO PCT Int. Appl., 19 pp.  
CODEN: PIXXD2  
DT Patent  
LA English  
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005094282	A2	20051013	WO 2005-US10152	20050325
WO 2005094282	A3	20060511		
W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW			
RW:	BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG			
EP 1804816	A2	20070711	EP 2005-745357	20050325
R:	AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LI, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR			
CN 101014353	A	20070808	CN 2005-80009262	20050325
US 20080025984	A1	20080131	US 2006-593217	20060915
PRAI US 2004-556565P	P	20040326		
WO 2005-1010152	W	20050325		
AB	The invention provides a method for treating tumor in a subject comprising administering to the subject an effective amount of (1) VNP40101M, or its equivalent; and (2) a nucleoside, or a nucleoside analog. The invention also provides a method for inhibiting tumor cell growth comprising contacting the tumor cell with effective amts. of: (1) VNP40101M, or its equivalent; and (2) a nucleoside, or a nucleoside analog. The invention relates to the treatment of cancer, comprising administering to a subject in need thereof an effective amount of VNP40101M in combination with a nucleoside.			

=> s Belcourt Michael/AU  
L12 6 BELCOURT MICHAEL/AU

=> dis l12 1-6 bib abs

L12 ANSWER 1 OF 6 CAPLUS COPYRIGHT 2008 ACS on STN  
AN 2005:1103438 CAPLUS  
DN 143:360090

TI Clotretazinetm (VNP40101M) combination with a nucleoside/nucleoside analog  
for cancer treatment  
IN King, Ivan; Sznol, Mario; Belcourt, Michael; Zheng, Li-Mou  
PA Vion Pharmaceuticals, Inc., USA  
SO PCT Int. Appl., 19 pp.  
CODEN: PIXXD2

DT Patent  
LA English

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2005094282	A2	20051013	WO 2005-US10152	20050325
	WO 2005094282	A3	20060511		
	W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW			
	RW:	BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG			
	EP 1804816	A2	20070711	EP 2005-745357	20050325
	R:	AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LI, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR			
	CN 101014353	A	20070808	CN 2005-80009262	20050325
	US 20080025984	A1	20080131	US 2006-593217	20060915
FRAI	US 2004-556565P	P	20040326		
	WO 2005-US10152	W	20050325		

AB The invention provides a method for treating tumor in a subject comprising administering to the subject an effective amount of (1) VNP40101M, or its equivalent; and (2) a nucleoside, or a nucleoside analog. The invention also provides a method for inhibiting tumor cell growth comprising contacting the tumor cell with effective amts. of: (1) VNP40101M, or its equivalent; and (2) a nucleoside, or a nucleoside analog. The invention relates to the treatment of cancer, comprising administering to a subject in need thereof an effective amount of VNP40101M in combination with a nucleoside.

L12 ANSWER 2 OF 6 CAPLUS COPYRIGHT 2008 ACS on STN

AN 2005:191780 CAPLUS

TI Hypoxia-selective anticancer agents: Phosphate derivatives of KS119 (VNP40119)

AU Lin, Xu Kevin; Belcourt, Michael; Zheng, Li-Mou; Clairmont, Caroline; Nassar, Ala; Doyle, Terrence W.; King, Ivan

CS Vion Pharmaceuticals Inc, New Haven, CT, 06511, USA

SO Abstracts of Papers, 229th ACS National Meeting, San Diego, CA, United States, March 13-17, 2005 (2005), MEDI-447 Publisher: American Chemical Society, Washington, D. C.

CODEN: 69GQMP

DT Conference; Meeting Abstract

LA English

AB It has been increasingly of interest that hypoxia-selective drugs play pos. roles in combining treatment with other clin. drug(s) or radiation for cancer therapy. More recently, we have developed a lead compound KS119 to address its hypoxia-selectivity from the class of the sulfonylhydrazine prodrugs (SHPs). In this unique sulfonylhydrazine class, CLORETAZINETM had been exhibited to be a novel alkylating agent for cancer therapy in Phase II human clin. trials; and it had been granted orphan drug designation from the FDA for treatment of acute myelogenous leukemia

(AML). In this presentation, design and synthesis of two lead series of phosphate derivs. (KS119W and KS119S) of KS119 will be shown. Preclin. investigation has demonstrated that these newly synthesized anticancer agents are highly hypoxia-selective and have a promising activity of tumor inhibition in vivo with excellent pharmaceutical and pharmacokinetic properties. These phosphate derivs. of KS119 are optimized to give a clin. candidate.

L12 ANSWER 3 OF 6 CAPLUS COPYRIGHT 2008 ACS on STN

AN 2003:169181 CAPLUS

DN 139:300968

TI Tumor-selective Salmonella-based cancer therapy

AU Bermudes, David; Low, K. Brooks; Pawelek, John; Feng, Ming; Belcourt,

Michael; Zheng, Li-Mou; King, Ivan

CS Vion Pharmaceuticals, Inc., New Haven, CT, 06511, USA

SO Biotechnology & Genetic Engineering Reviews (2001), 18, 219-233

CODEN: BGERES; ISSN: 0264-8725

PB Intercept Ltd.

DT Journal; General Review

LA English

AB A review of tumor-selective Salmonella-based cancer therapy includes subtopics of (1) introduction (2) genetic methods for generation of tumor-specific strains (3) antitumor efficacy of VNP 20009 (4) tumor-specific prodrug -converting enzyme delivery (5) antitumor effects of Salmonella in combination with radiation (6) conclusions.

RE.CNT 41 THERE ARE 41 CITED REFERENCES AVAILABLE FOR THIS RECORD

ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 4 OF 6 CAPLUS COPYRIGHT 2008 ACS on STN

AN 2002:526744 CAPLUS

DN 138:247993

TI Tumor-targeted Salmonella expressing cytosine deaminase as an anticancer agent

AU King, Ivan; Bermudes, David; Lin, Stanley; Belcourt, Michael;

Pike, Jeremy; Troy, Kimberly; Le, Trung; Ittensohn, Martina; Mao, John;

Lang, Wenshang; Runyan, Jacob D.; Luo, Xiang; Li, Zujin; Zheng, Li-Mou

CS Vion Pharmaceuticals, Inc., New Haven, CT, 06511, USA

SO Human Gene Therapy (2002), 13(10), 1225-1233

CODEN: HGTHE3; ISSN: 1043-0342

PB Mary Ann Liebert, Inc.

DT Journal

LA English

AB The study was designed to evaluate whether TAPET-CD, an attenuated strain of Salmonella typhimurium expressing Escherichia coli cytosine deaminase (CD), was capable of converting nontoxic 5-fluorocytosine (5-FC) to the active antitumor agent 5-fluorouracil (5-FU). The antitumor effect of TAPET-CD plus 5-FC against s.c. implanted colon tumors was also evaluated. TAPET-CD was given to tumor-bearing mice by a single bolus i.v. administration followed with 5-FC by i.p. administration. TAPET-CD accumulated in tumors at levels 1000-fold higher than that in normal tissues and high levels of 5-FU were detected in tumors in mice treated with both TAPET-CD and 5-FC. No 5-FU could be detected in normal tissues. Inhibition of tumor growth was observed in mice treated with either TAPET-CD alone or TAPET-CD in combination with 5-FC (TAPET-CD/5-FC), but not with 5-FC alone. TAPET-CD/5-FC inhibited tumor growth by 88%-96%, compared to TAPET-CD alone, which inhibited tumor growth by 38%-79%. These data suggest that tumor-targeting Salmonella could be used to deliver prodrug-converting enzyme selectively to tumors and produced anti-tumor effects when the corresponding prodrug was also given.

RE.CNT 22 THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS RECORD

ALL CITATIONS AVAILABLE IN THE RE FORMAT



L12 ANSWER 5 OF 6 CAPLUS COPYRIGHT 2008 ACS on STN  
 AN 2001:265561 CAPLUS  
 DN 134:290399  
 TI Compositions and methods for tumor-targeted delivery of effector molecules  
 IN Bermudes, David G.; King, Ivan C.; Clairmont, Caroline A.; Lin, Stanley  
 L.; Belcourt, Michael  
 PA Vion Pharmaceuticals, Inc., USA  
 SO PCT Int. Appl., 185 pp.  
 CODEN: PIXXD2  
 DT Patent  
 LA English  
 FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2001025397	A2	20010412	WO 2000-US23242	20000824
	WO 2001025397	A3	20020124		
	W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW			
	RW:	GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG			
	CA 2386465	A1	20010412	CA 2000-2386465	20000824
	AU 2000069334	A	20010510	AU 2000-69334	20000824
	AU 783714	B2	20051201		
	EP 1261369	A2	20021204	EP 2000-957764	20000824
	R:	AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL			
	JP 2004500042	T	20040108	JP 2001-528552	20000824
	BR 2000014491	A	20040309	BR 2000-14491	20000824
	NZ 518354	A	20050225	NZ 2000-518354	20000824
	US 6962696	B1	20051108	US 2000-645415	20000824
	MX 2002PA03384	A	20020820	MX 2002-PA3384	2020403
	US 20040229338	A1	20041118	US 2003-738423	20031216
	US 20050249706	A1	20051110	US 2005-82544	20050317
	US 20070298012	A1	20071227	US 2007-627743	20070126
PRAI	US 1999-157500P	P	19991004		
	US 1999-157581P	P	19991004		
	US 1999-157637P	P	19991004		
	US 2000-645415	A3	20000824		
	WO 2000-US23242	W	20000824		
	US 2003-738423	A1	20031216		

AB The present application discloses the preparation and use of attenuated tumor-targeted bacteria vectors for the delivery of one or more primary effector mol.(s) to the site of a solid tumor. The primary effector mol.(s). of the invention is used in the methods of the invention to treat a solid tumor cancer such as a carcinoma, melanoma, lymphoma, or sarcoma. The invention relates to the surprising discovery that effector mols., which may be toxic when administered systemically to a host, can be delivered locally to tumors by attenuated tumor-targeted bacteria with reduced toxicity to the host. The application also discloses the delivery of one or more optional effector mol.(s) (termed secondary effector mols.) which may be delivered by the attenuated tumor-targeted bacteria in conjunction with the primary effector mol.(s).

L12 ANSWER 6 OF 6 CAPLUS COPYRIGHT 2008 ACS on STN  
 AN 1989:626082 CAPLUS

DN 111:226082  
 OREF 111:37409a,37412a  
 TI Enhancer and silencerlike sites within the transcribed portion of a Ty2 transposable element of *Saccharomyces cerevisiae*  
 AU Farabaugh, Philip; Liao, Xiao Bei; Belcourt, Michael; Zhao, Hong; Kapakos, James; Clare, Jeffrey  
 CS Dep. Biol. Sci., Univ. Maryland, Catonsville, MD, 21228, USA  
 SO Molecular and Cellular Biology (1989), 9(11), 4824-34  
 CODEN: MCEBD4; ISSN: 0270-7306  
 DT Journal  
 LA English  
 AB The Ty2-917 element is a member of the Ty2 class of retroviruslike transposable elements of *S. cerevisiae*. Regions downstream of the Ty2-917 transcription start site modulate its transcription. One region was located downstream of the transcription initiation site (position 240) and within the first 559 base pairs of the element. This region had a dramatic effect, causing an approx. 1000-fold increase in steady-state levels of RNA. The region stimulated transcription when placed in either orientation upstream of a heterologous gene, *HIS4*, lacking its own upstream activation sequence (UAS). This pos. acting region was termed an enhancer, by analogy to sites described in higher cells, to distinguish it from yeast UASs which do not function when placed within the transcribed portion of the gene. Though, like some higher eukaryotic enhancers, the Ty2-917 enhancer is located within the transcribed region, it is unlike them in that it occurs within a coding region rather than in an intron. The Ty2-917 enhancer and the Ty2-917 UAS had a synergistic effect on transcription, together stimulating transcription 15-fold over the predicted additive effect. The authors also identified a site which decreases RNA accumulation, located about 750 base pairs into the element. This site functioned in only one orientation when inserted upstream of the UAS-less heterologous gene. The site was similar to silencers, or neg. enhancers, in that it acted to repress transcription from outside the transcribed region, but was distinct in that the function of a canonical silencer was independent of orientation.

=> s Zheng Li-Mou/AU  
 L13 32 ZHENG LI-MOU/AU

=> s l13 and choretazine  
 0 CHORETAZINE  
 L14 0 L13 AND CHORETAZINE

=> s l13 and cloretazine  
 21 CLORETAZINE  
 L15 2 L13 AND CLORETAZINE

=> dis l15 1-2 bib abs

L15 ANSWER 1 OF 2 CAPLUS COPYRIGHT 2008 ACS on STN  
 AN 2007:447320 CAPLUS  
 DN 147:180783  
 TI Anti-tumor efficacy of Cloretazine (VNP40101M) alone and in combination with fludarabine in murine tumor and human xenograft tumor models  
 AU Zheng, Li-mou; Li, Zujin; Liu, Lanzhen; Song, Bai Louis; King, Ivan  
 CS Vion Pharmaceutical, Inc., New Haven, CT, 06511, USA  
 SO Cancer Chemotherapy and Pharmacology (2007), 60(1), 45-51  
 CODEN: CCPHDZ; ISSN: 0344-5704  
 PB Springer

DT Journal  
 LA English  
 AB Cloretazine (VNP40101M), a new sulfonylhydrazine alkylating agent, has demonstrated broad-spectrum anti-tumor activity in preclin. studies. In this study, Cloretazine was evaluated both as a monotherapy and in combination with fludarabine in murine tumor and human tumor xenograft models. Cloretazine significantly inhibited the growth of s.c. implanted tumors, including B16F10 murine melanoma in C57BL/6 mice, and H460 human lung carcinoma and WiDr human colon carcinoma in athymic nude CD1 mice. The inhibition of tumor growth by Cloretazine was dose dependent, increasing from 42.2 to 87% as the dose escalated from 100 to 150 mg/kg. Cloretazine showed equivalent efficacy but lower toxicity compared to cyclophosphamide in these models. The combination therapy, consisting of a single dose of 10 mg/kg Cloretazine plus five doses of 70 mg/kg fludarabine, given every other day i.p., significantly increased the long-term survival of BDF1 mice bearing the L1210 murine leukemia. On Day 65 post-tumor implantation, the combination therapy yielded a 90% survival rate compared to 40% for Cloretazine alone and 0% for fludarabine alone.

RE.CNT 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS RECORD  
 ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15 ANSWER 2 OF 2 CAPLUS COPYRIGHT 2008 ACS on SIN  
 AN 2005:1103438 CAPLUS  
 DN 143:360090  
 TI Cloretazineta (VNP40101M) combination with a nucleoside/nucleoside analog for cancer treatment  
 IN King, Ivan; Sznol, Mario; Belcourt, Michael; Zheng, Li-Mou  
 PA Vion Pharmaceuticals, Inc., USA  
 SO PCT Int. Appl., 19 pp.  
 CODEN: PIXXD2

DT Patent  
 LA English

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2005094282	A2	20051013	WO 2005-US10152	20050325
	WO 2005094282	A3	20060511		
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
	RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
EP	1804816	A2	20070711	EP 2005-745357	20050325
	R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LI, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR				
	CN 101014353	A	20070808	CN 2005-80009262	20050325
	US 20080025984	A1	20080131	US 2006-593217	20060915
PRAI	US 2004-556565P	P	20040326		
	WO 2005-US10152	W	20050325		
AB	The invention provides a method for treating tumor in a subject comprising administering to the subject an effective amount of (1) VNP40101M, or its equivalent; and (2) a nucleoside, or a nucleoside analog. The invention also provides a method for inhibiting tumor cell growth comprising contacting the tumor cell with effective amts. of: (1) VNP40101M, or its equivalent; and				

(2) a nucleoside, or a nucleoside analog. The invention relates to the treatment of cancer, comprising administering to a subject in need thereof an effective amount of VNP40101M in combination with a nucleoside.

=> dis hist

(FILE 'HOME' ENTERED AT 13:39:43 ON 07 MAY 2008)

FILE 'APOLLIT, BABS, CAPLUS, CBNB, CIN, COMPENDEX, DISSABS, EMA, IFIPAT, NTIS, PASCAL, PROMT, RAPRA, SCISEARCH, TEXTILETECH, USPATFULL, USPATOLD, USPAT2, WPIFV, WPINDEX, WSCA, WTEXTILES, BIOSIS, EMBASE, MEDLINE' ENTERED AT 13:41:01 ON 07 MAY 2008

L1 0 S VNP40110M  
L2 17 S METHYLAMINOCARBONYL(A)HYDRAZINE  
L3 17 S L2 AND VNP40101M  
L4 17 S L3 AND (TUMOR OR ANTITUMOR)  
L5 2 S L4 AND NUCLEOSIDE

FILE 'CAPLUS' ENTERED AT 13:45:02 ON 07 MAY 2008

L6 42 S KING IVAN/AU  
L7 0 S L6 AND CHLORETAZINE  
L8 0 S L7 AND CLORETAZINE  
L9 3 S L6 AND CLORETAZINE  
L10 30 S SZNOL MARIO/AU  
L11 2 S L10 AND CLORETAZINE  
L12 6 S BELCOURT MICHAEL/AU  
L13 32 S ZHENG LI-MOU/AU  
L14 0 S L13 AND CHORETAZINE  
L15 2 S L13 AND CLORETAZINE

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